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Original Review Article

Plurethosomal Nanocarriers As A Promising Platform For Arnebin-1 Delivery In Wound Healing Therapy: A Comprehensive Review

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Abstract: Wound healing is a complex physiological process that includes inflammation, tissue regeneration, angiogenesis, and extracellular matrix modification. Chronic wounds continue to pose a significant healthcare burden because to delayed healing, infection, and the limited efficacy of current therapy. Herbal bioactive chemicals are increasingly being investigated due to their medicinal potential and minimal toxicity. Arnebin-1, a natural naphthoquinone found in Arnebia species, has potent wound healing, anti-inflammatory, antioxidant, and antibacterial properties. However, its clinical applicability is limited due to weak water solubility, instability, and low skin permeability. Nanotechnology-based drug delivery systems, particularly plurethosomal nanocarriers, present a promising option by improving drug loading, stability, flexibility, and epidermal penetration. This review focuses on the therapeutic role of Arnebin-1, plurethosome formulation strategies, dermal delivery routes, characterisation methodologies, benefits, limits, and future opportunities in wound healing therapy.

Keywords: Arnebin-1, Plurethosomes, Wound Healing, Nanocarriers, Herbal Drug Delivery, Vesicular Systems, Topical Nanomedicine.

1. Introduction

Skin is the primary protective barrier of the human body against external diseases, environmental pollutants, and physical injuries. Damage to skin integrity sets off a complicated chain of biological reactions that include hemostasis, inflammation, proliferation, and tissue remodeling. Wound healing needs a coordinated cellular and molecular response involving fibroblasts, keratinocytes, inflammatory mediators, and extracellular matrix proteins. Impaired wound healing can cause chronic ulcers, infections, and tissue necrosis, lowering patient quality of life and raising healthcare costs.

Conventional wound healing therapies, such as ointments, creams, and bandages, frequently exhibit inadequate penetration, limited retention, and uneven therapeutic efficacy. Additionally, continuous usage of synthetic medications may result in side effects and antimicrobial resistance. As a result, there is increased interest in plant-derived bioactive molecules having multifunctional medicinal properties.

Arnebia euchroma and allied medicinal plants in the Boraginaceae family are the source of Arnebin-1, a promising phytoconstituent. These herbs have historically been used to treat skin conditions, burns, wounds, and inflammation. Through the activation of fibroblast proliferation, collagen synthesis, angiogenesis, and antioxidant defense mechanisms, Arnebin-1 has been shown in contemporary pharmacological studies to have strong wound healing action.

Arnebin-1 has limited bioavailability and poor water solubility, which limits its clinical use despite its medicinal potential. In order to enhance its therapeutic efficacy, nanocarrier-based delivery techniques have been studied. Phospholipids, ethanol, and pluronic copolymers make up the sophisticated vesicular system known as plurethosomal nanocarriers, which enable improved skin penetration and regulated medication release. They are appropriate for the topical administration of hydrophobic herbal substances because to their distinct structure and physicochemical properties.

2. Literature Review

Wound Healing Process

The physiological process of wound healing is dynamic, highly regulated, and involves several overlapping stages. In order to stop blood loss, platelet aggregation and clot formation take place in the first stage, hemostasis, which happens right after damage. After that comes the inflammatory phase, which is marked by the influx of neutrophils and macrophages that get rid of pathogens and cell debris.

Granulation tissue development, angiogenesis, collagen deposition, and fibroblast migration are all part of the proliferative phase. During this stage, skin integrity is restored through keratinocyte proliferation and epithelialization. Collagen maturation and scar tissue formation are the final stages of the remodeling phase, which restores the strength and functionality of the tissue.

Age, nutrition, infection, diabetes, vascular insufficiency, and oxidative stress are some of the variables that affect wound healing. Prolonged inflammation and increased production of reactive oxygen species are common in chronic wounds, which impede tissue healing. For efficient wound care, therapeutic substances with anti-inflammatory, antioxidant, and antibacterial properties are therefore particularly desirable.

Arnebin-1: Source And Pharmacological Activities

The roots of Arnebia euchroma are the main source of arnebin-1, a bioactive naphthoquinone derivative. Arnebia preparations have long been used in traditional medicine to treat inflammatory conditions and skin lesions. Research has shown that Arnebin-1 has a wide range of pharmacological properties that are pertinent to the treatment of wound healing.

Arnebin-1 promotes tissue regeneration by increasing collagen synthesis and fibroblast proliferation. Additionally, it speeds up angiogenesis, which enhances the wound site's availability of nutrients and oxygen. By scavenging reactive oxygen species and shielding cellular structures, Arnebin-1's antioxidant action lessens oxidative damage.

The substance also exhibits antibacterial activity against a number of diseases linked to wounds. Modulation of inflammatory cytokines and suppression of signaling pathways implicated in tissue damage are the mechanisms by which anti-inflammatory actions are mediated. Together, these multipurpose processes improve tissue remodeling, epithelialization, and wound contraction.

However, Arnebin-1's solubility and skin penetration are restricted by its hydrophobic nature. Its therapeutic efficacy is further diminished by instability during storage and quick breakdown under physiological settings. These restrictions call for the creation of sophisticated drug delivery methods that can improve stability and bioavailability.

Nanotechnology In Wound Healing

Because nanotechnology allows for controlled and targeted medication delivery, it has transformed pharmaceutical and biomedical research. While reducing systemic toxicity, nanocarrier systems enhance the pharmacokinetic and pharmacodynamic characteristics of therapeutic drugs. Nanotechnology promotes improved skin penetration, prolonged medication release, hydration retention, and antibacterial protection in wound healing applications.

Liposomes, niosomes, ethosomes, transferosomes, solid lipid nanoparticles, and polymeric nanoparticles are among the nanocarriers that have been studied for topical medication administration. Because vesicular systems are biocompatible and can encapsulate both hydrophilic and hydrophobic substances, they are very beneficial.

The advantages of ethosomes and pluronic polymers are combined in plurethosomes, a modified vesicular system. These nanocarriers have better transdermal penetration, increased stability, and greater deformability. They are ideal for wound healing applications because of their capacity to encapsulate hydrophobic phytoconstituents like Arnebin-1

Plurethosomal Nanocarriers

Phospholipids, ethanol, water, and pluronic block copolymers combine to form nanoscale vesicular structures known as plurethosomes. Deeper skin penetration is made possible by ethanol's increased membrane fluidity and disruption of the stratum corneum's lipid structure. Pluronic copolymers increase vesicle flexibility and offer steric stability.

Plurethosomes exhibit greater entrapment efficiency, better physical stability, and increased permeability as compared to traditional liposomes. Because of their deformability, they can move effectively across intercellular channels and tiny skin pores. Additionally, these vesicles prolong therapeutic activity at the wound site by releasing encapsulated medications in a sustained manner.

Enhanced transdermal distribution is facilitated by the synergistic interaction between ethanol and pluronic polymers. While pluronic polymers decrease vesicle aggregation and enhance colloidal stability, ethanol fluidizes epidermal and vesicular lipids. Plurethosomes are interesting carriers for topical herbal medication delivery because of their characteristics.

Formulation Approaches

Plurethosomal formulations are prepared using a variety of procedures, such as thin-film hydration, ethanol injection, sonication, and reverse-phase evaporation. Vesicle properties and therapeutic efficacy are greatly influenced by the choice of formulation ingredients and process variables.

The efficiency of drug encapsulation and vesicle production are influenced by phospholipid content. Pluronic polymer concentration affects stability and deformability, whereas ethanol concentration affects skin penetration and membrane fluidity. To achieve consistent nanosized vesicles, sonication time and hydration conditions must be optimized.

Phosphatidylcholine, ethanol, and pluronic F127 or F68 are typically used in the formulation of arnebin-1 loaded plurethosomes. To increase topical retention and patient compliance, the produced vesicles could be added to hydrogel systems. Incorporating hydrogel also creates a moist environment that promotes wound healing.

3. Best Formulation And Characterization Of Arnebin-1 Loaded Plurethosomal Gel

Rationale For Optimized Formulation

Arnebin-1, a bioactive naphthoquinone isolated from *Arnebia euchroma*, exhibits significant therapeutic potential in wound healing due to its anti-inflammatory, antioxidant, and regenerative properties. However, its clinical applicability is considerably restricted by poor aqueous solubility, hydrophobic nature, and limited skin permeability.

To overcome these limitations, the development of an optimized plurethosomal gel system is essential. Plurethosomes, owing to their unique composition of phospholipids, ethanol, and pluronic polymers, enhance drug solubilization, improve dermal penetration, and provide sustained release, thereby significantly improving the therapeutic performance of Arnebin-1 in topical applications.

Optimized Formulation Composition

An ideal Arnebin-1 loaded plurethosomal gel formulation comprises carefully selected components that synergistically contribute to vesicle formation, stability, and drug delivery efficiency:

- **Phospholipids (e.g., Phosphatidylcholine):** Form the structural bilayer of vesicles, facilitating encapsulation of lipophilic drug molecules
- **Pluronic block copolymers (F127/F68):** Provide steric stabilization, enhance deformability, and prevent vesicle aggregation
- **Cholesterol:** Improves membrane rigidity and enhances structural stability of vesicles
- **Ethanol (20–40%):** Acts as a permeation enhancer by fluidizing lipid bilayers and increasing skin penetration
- **Aqueous phase (buffer pH 5.5–6.5):** Maintains physiological compatibility with skin
- **Gelling agents (Carbopol 934 or HPMC):** Impart suitable viscosity, spreadability, and patient acceptability

Method of Preparation

The preparation of Arnebin-1 loaded plurethosomal systems typically involves established vesicular fabrication techniques, including:

- Thin-film hydration method
- Ethanol injection method
- Probe sonication for reduction of vesicle size to nanoscale

Following vesicle formation, the dispersion is incorporated into a suitable gel base under controlled pH conditions to obtain a stable and homogenous topical formulation. This approach ensures improved drug retention at the application site and enhances patient compliance.

Critical Formulation Parameters

The performance and efficiency of the plurethosomal formulation are highly dependent on various formulation and process variables:

- **Lipid concentration:** Influences vesicle formation and drug encapsulation efficiency
- **Ethanol content:** Determines membrane fluidity and transdermal permeation
- **Polymer concentration:** Affects vesicle stability, deformability, and steric hindrance
- **Sonication time:** Plays a crucial role in controlling particle size and distribution

Optimization of these parameters is essential to achieve reproducible and high-performance formulations.

Detailed Characterization Of Arnebin-1 Formulation

Comprehensive characterization is essential to evaluate the quality, stability, and therapeutic potential of the developed formulation.

(A) Vesicle Characterization

- **Particle Size (100–300 nm):** Determined using Dynamic Light Scattering (DLS); smaller vesicles enhance skin penetration
- **Polydispersity Index (PDI < 0.3):** Indicates uniformity of size distribution
- **Zeta Potential (±20 mV):** Reflects colloidal stability and prevents aggregation

(B) Morphological Analysis

- Transmission Electron Microscopy (TEM)
- Scanning Electron Microscopy (SEM)

These techniques confirm vesicle shape, surface characteristics, and lamellarity, typically revealing spherical and well-defined vesicular structures.

(C) Entrapment Efficiency (EE%)

Entrapment efficiency is a critical parameter indicating the drug-loading capacity of the vesicular system:

Higher entrapment efficiency (>70%) signifies effective incorporation of Arnebin-1 within the vesicles.

(D) Physicochemical Evaluation of Gel

- **pH:** Maintained within the range of 5.5–6.5 for skin compatibility
- **Viscosity:** Measured using Brookfield viscometer to ensure optimal consistency
- **Spreadability:** Determines ease of application
- **Drug content uniformity:** Ensures consistent dosing

(E) In Vitro Drug Release Study

- Conducted using Franz diffusion cell
- Demonstrates controlled and sustained drug release behavior
- Release kinetics typically follow Higuchi or Korsmeyer–Peppas models

(F) Ex Vivo Skin Permeation Study

- Performed using excised animal or human skin
- Evaluates:
    - Drug flux
    - Permeability coefficient
    - Skin retention capacity

These studies provide insight into the transdermal delivery efficiency of the formulation.

(G) Stability Studies

Stability assessment is conducted as per ICH guidelines to evaluate formulation robustness over time:

- Monitoring changes in particle size
- Drug content analysis
- Physical appearance and phase separation

4. Significance Of Optimized Formulation

The development of an optimized Arnebin-1 loaded plurethosomal gel offers several therapeutic and pharmaceutical advantages:

- Enhanced bioavailability of poorly soluble drug
- Improved dermal penetration and retention
- Sustained and controlled drug release
- Accelerated wound healing efficacy
- Reduced frequency of administration and improved patient compliance

5. Characterization Of Plurethosomal Systems

Evaluating plurethosomal formulations' quality, stability, and therapeutic efficacy requires thorough characterization. Dynamic light scattering techniques are frequently used for particle size analysis. Improved skin penetration and consistent medication distribution are made possible by smaller vesicle sizes. Zeta potential gives information about colloidal stability, while polydispersity index shows homogeneity in size distribution. Reduced vesicle aggregation is typically indicated by high absolute zeta potential values.

Transmission electron microscopy or scanning electron microscopy are used for morphological evaluation. The amount of medication that is successfully contained within vesicles is determined by entrapment efficiency experiments. Drug-excipient compatibility and physicochemical interactions are examined using Fourier transform infrared spectroscopy and differential scanning calorimetry.

Ex vivo permeation studies employing Franz diffusion cells measure transdermal transport efficiency, whereas in vitro drug release studies examine sustained release behavior. To ascertain the shelf life of a formulation, stability tests are also carried out under various storage settings.

Mechanism Of Enhanced Wound Healing

Through a variety of ways, plurethosomal delivery systems enhance wound healing. Their nanoscale size facilitates effective distribution of Arnebin-1 to the target region by improving penetration into deeper epidermal layers. Long-term therapeutic action is guaranteed by sustained release behavior, which also lowers the frequency of dose. Antioxidant action mediated by arnebin-1 reduces oxidative stress, shielding cells from harm caused by free radicals. Excessive cytokine synthesis and inflammatory cell infiltration are decreased by anti-inflammatory action. Rapid tissue regeneration and wound contraction are facilitated by increased collagen production and fibroblast proliferation.

Additionally, plurethosomal formulations enhance the absorption of hydrophobic substances and preserve hydration at the wound site. Together, increased angiogenesis and epithelialization speed up tissue remodeling and skin integrity restoration.

6. Advantages And Limitations

Compared to traditional topical preparations, plurethosomal systems provide a number of advantages. Increased skin penetration lowers the necessary medication dosage and improves therapeutic efficacy. Sustained drug release increases patient adherence and reduces the need for frequent administration. Their medicinal value is further enhanced by their excellent encapsulation efficiency and improved stability.

However, plurethosomal systems still have some drawbacks. Sensitive people may occasionally experience skin irritation due to high ethanol concentrations. Reproducibility of formulations and large-scale manufacturing are still difficult. Nanomedicine regulatory approval procedures are likewise complicated and necessitate thorough safety assessment.

Despite these drawbacks, it is anticipated that ongoing developments in pharmaceutical engineering and nanotechnology will enable the successful clinical translation of plurethosomal formulations.

Arnebin-1 In Gel Form Versus Other Dosage Forms

Arnebin-1, when formulated into gel-based systems such as hydrogels or plurethosomal gels, demonstrates superior therapeutic efficacy compared to conventional dosage forms like ointments, creams, and solutions. This enhanced performance can be attributed to the unique physicochemical and biopharmaceutical properties of gel systems.

Gel formulations offer improved patient acceptability due to their non-greasy texture and ease of application. Additionally, they maintain a moist environment at the wound site, which is crucial for accelerating epithelialization and overall wound healing. The increased residence time of the formulation on the skin further contributes to enhanced drug retention and localized action.

Another significant advantage of gel systems is their ability to provide controlled and sustained drug release. When combined with advanced nanocarriers such as plurethosomes, gels facilitate deeper skin penetration and improved drug bioavailability. Furthermore, gels are generally associated with reduced irritation compared to ointments, as they are less occlusive in nature.

From a mechanistic perspective, gel matrices create an optimal microenvironment for wound healing by maintaining hydration, enabling diffusion-controlled drug release, and prolonging drug–skin contact time.

Mechanism Of Action Of Arnebin-1

Arnebin-1 exhibits a broad spectrum of pharmacological activities that collectively contribute to its wound healing potential.

It exerts a strong anti-inflammatory effect by inhibiting pro-inflammatory cytokines such as TNF-α and IL-6, while also suppressing the NF-κB signaling pathway. In addition, Arnebin-1 demonstrates significant antioxidant activity by scavenging reactive oxygen species (ROS), thereby protecting cellular components from oxidative damage.

The compound also promotes fibroblast migration and proliferation, enhancing collagen synthesis. Furthermore, it stimulates angiogenesis through the upregulation of VEGF, leading to improved oxygen and nutrient supply at the wound site.

Arnebin-1 also exhibits antibacterial properties by disrupting microbial cell membranes, thereby reducing the risk of wound infection and supporting faster healing.

7. Differentiation Of Plurethosomes From Other Vesicular Systems

Plurethosomes represent an advanced class of vesicular drug delivery systems that integrate the advantages of liposomes, ethosomes, and polymeric carriers.

Conventional liposomes are limited by poor skin penetration and low deformability. Ethosomes enhance penetration due to ethanol but often suffer from stability issues. Transferosomes provide high deformability but may have reduced stability during storage.

In contrast, plurethosomes consist of phospholipids, ethanol, and pluronic polymers, resulting in enhanced deformability and stability. They show higher drug entrapment efficiency and improved transdermal delivery. Pluronic polymers provide steric stabilization, reducing vesicle aggregation.

A key distinguishing feature is the synergistic interaction between ethanol and pluronic polymers, where ethanol enhances membrane fluidity and polymers improve stability.

Specific Advantages Of Arnebin-1

Arnebin-1 is particularly well-suited for delivery via plurethosomal systems due to its hydrophobic nature, which allows efficient incorporation into lipid vesicles.

It exhibits multifunctional therapeutic activity including anti-inflammatory, antioxidant, and antibacterial effects, enabling it to target multiple stages of wound healing. It also enhances collagen synthesis and tissue regeneration.

Nanocarrier-based delivery improves its efficacy even at lower doses, reducing potential side effects. Clinically, Arnebin-1 addresses oxidative stress, infection, and prolonged inflammation in chronic wounds.

8. Future Perspectives

Subsequent studies ought to concentrate on creating sophisticated surface-modified plurethosomes that can transport drugs in a targeted and stimuli-responsive manner. Adding growth factors, peptides, and bioactive polymers may improve the effectiveness of wound healing even further. Commercial development requires clinical trials assessing treatment outcomes and safety in patients with chronic wounds.

Optimized formulation design and drug release behavior prediction may potentially benefit from computer modeling and artificial intelligence. Arnebin-1 and other phytoconstituents may have synergistic therapeutic effects when used in combination therapy. A possible path for next-generation wound care treatments is the combination of nanotechnology and herbal medicine.

9. Current Research Gaps

There are still a number of obstacles in the development of Arnebin-1-loaded plurethosomal nanocarriers, despite advancements in nanotechnology-based wound healing systems. There are few well-designed clinical trials evaluating long-term safety and efficacy in humans, and the majority of research is restricted to in vitro and animal studies. There is a lack of toxicological information about systemic absorption, long-term exposure, and nanoparticle accumulation. The need for standardized protocols is highlighted by the inconsistent performance caused by variations in formulation components and preparation techniques. Furthermore, it is unclear what molecular processes underlie Arnebin-1's therapeutic actions. Despite their therapeutic significance, there is little research on diabetic and chronic wounds. Moreover, commercialization and extensive clinical use of these sophisticated nanocarrier systems are hampered by issues with large-scale production, repeatability, and regulatory approval.

10. Major Challenges In Plurethosomal Wound Healing Systems

There are still a number of obstacles in the development of Arnebin-1-loaded plurethosomal nanocarriers, despite advancements in nanotechnology-based wound healing systems. There are few well-designed clinical trials evaluating long-term safety and efficacy in humans, and the majority of research is restricted to in vitro and animal studies. There is a lack of toxicological information about systemic absorption, long-term exposure, and nanoparticle accumulation. The need for standardized protocols is highlighted by the inconsistent performance caused by variations in formulation components and preparation techniques. Furthermore, it is unclear what molecular processes underlie Arnebin-1's therapeutic actions. Despite their therapeutic significance, there is little research on diabetic and chronic wounds. Moreover, commercialization and extensive clinical use of these sophisticated nanocarrier systems are hampered by issues with large-scale production, repeatability, and regulatory approval.

11 Suggestions And Recommendations For Future Research

Future studies should concentrate on creating sophisticated plurethosomal systems with better efficiency and targeting. Controlled medication release at wound sites can be made possible by smart stimuli-responsive carriers (pH, ROS, enzyme, or temperature-sensitive). Targeting, retention, and cellular absorption may be improved by surface modification with ligands, peptides, or polymers. Synergistic effects could be achieved by combining Arnebin-1 with growth hormones, exosomes, or antimicrobial drugs in combination therapy. Drug release behavior prediction and formulation optimization can be aided by artificial intelligence. Sustained release and patient compliance could be enhanced by incorporation into sophisticated hydrogels. Additionally promising are customized wound treatment strategies based on patient-specific circumstances. Long-term clinical trials are also necessary to prove efficacy and safety. The use of biodegradable and environmentally friendly materials in green nanotechnology will further improve sustainability and lower toxicity.

12. Conclusion

A promising method for efficiently delivering Arnebin-1 in wound healing therapy is plurethosomal nanocarriers. The therapeutic effectiveness of hydrophobic phytoconstituents is greatly boosted by their improved flexibility, excellent penetration capability, high encapsulation efficiency, and sustained release properties. Strong wound-healing, anti-inflammatory, antioxidant, and antibacterial properties of arnebin-1 promote tissue regeneration and repair. Innovative possibilities for safer and more efficient wound care are presented by the integration of cutting-edge nanovesicular systems with herbal bioactive substances. Plurethosomal formulations may prove to be beneficial substitutes for traditional wound healing treatments with more investigation and clinical validation.

13. Figures

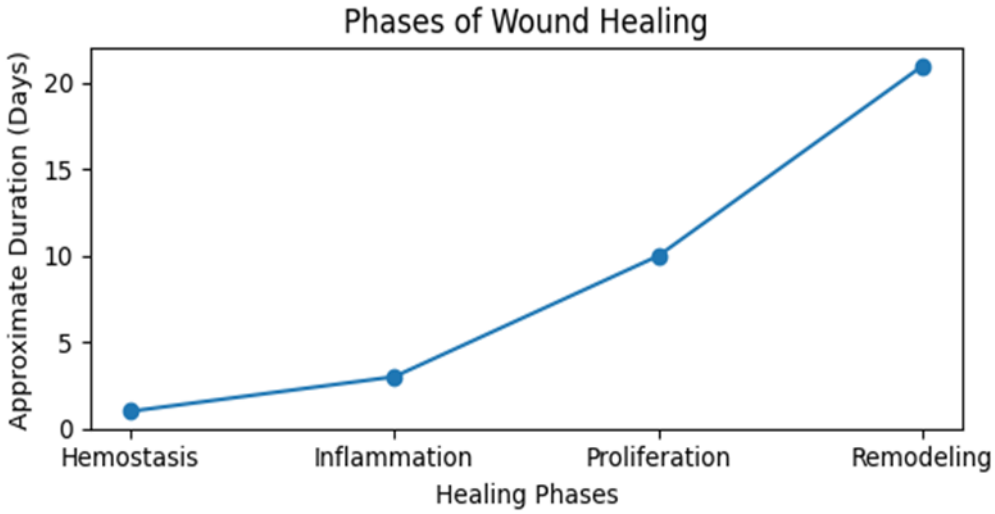

Figure 1. Sequential phases involved in wound healing.

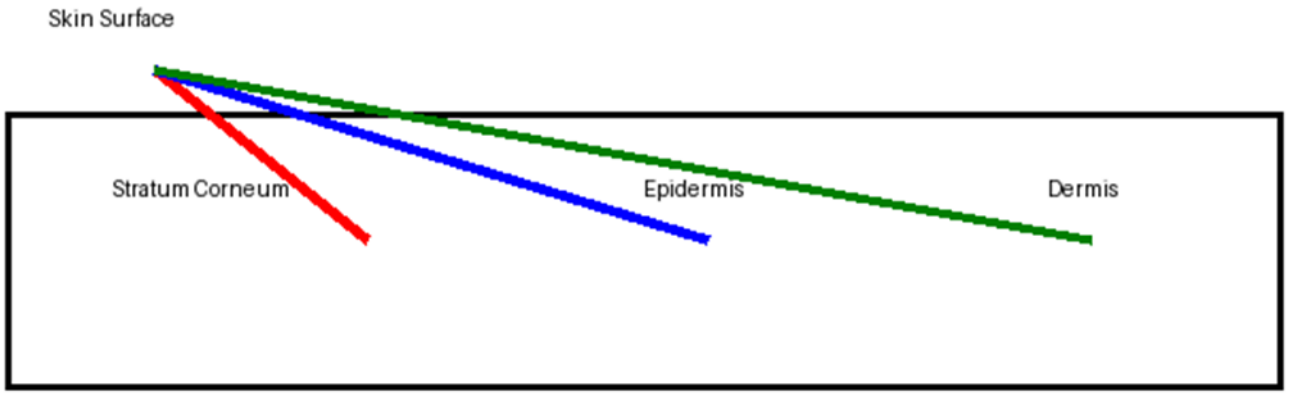

Figure 2. Schematic representation of plurethosomal penetration through skin layers.

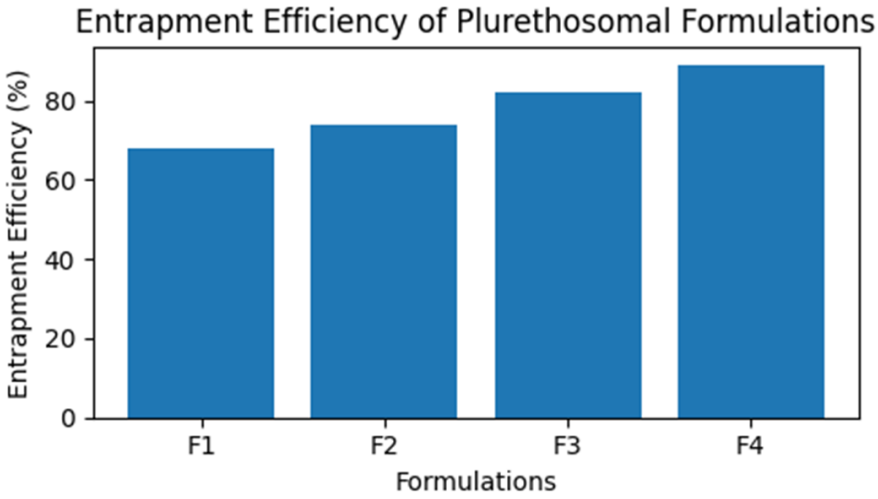

Figure 3. Comparative entrapment efficiency of optimized plurethosomal formulations.

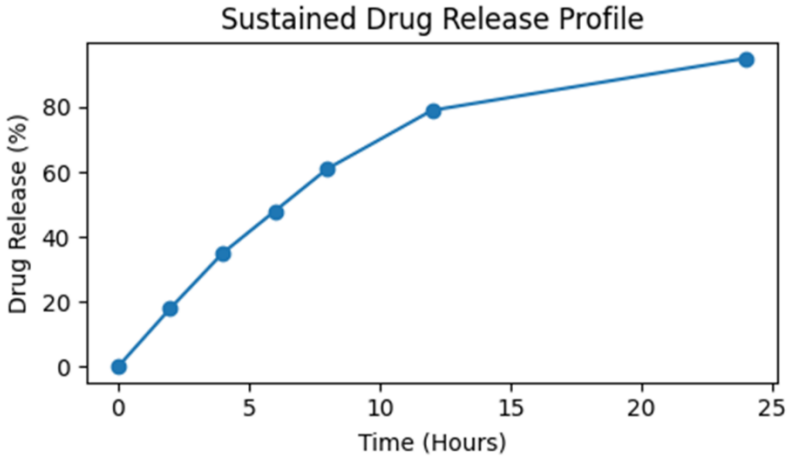

Figure 4. Sustained release profile of Arnebin-1 from plurethosomal vesicles.

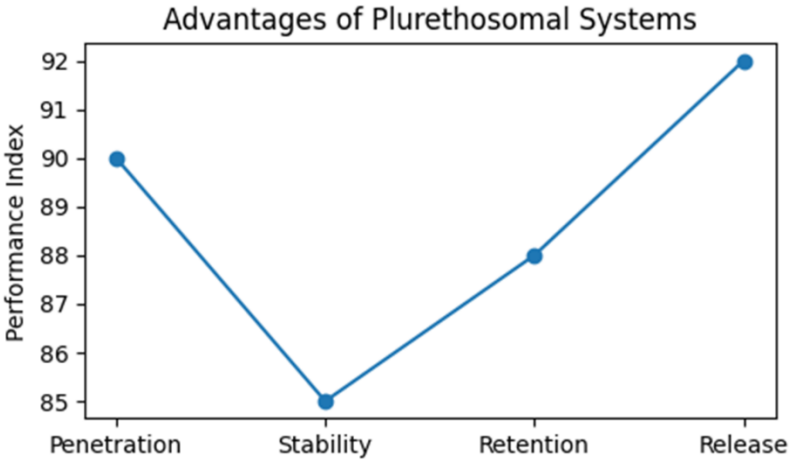

Figure 5. Functional advantages associated with plurethosomal nanocarriers.

14. Tables

Table 1. Stages of wound healing and associated biological events

Stage	Major Events
Hemostasis	Platelet aggregation and clot formation
Inflammation	Neutrophil and macrophage infiltration
Proliferation	Fibroblast migration and collagen deposition
Remodeling	Scar maturation and tissue strengthening

Table 2. Pharmacological activities of Arnebin-1

Activity	Therapeutic Effect
Anti-inflammatory	Reduces cytokine-mediated damage
Antioxidant	Scavenges reactive oxygen species
Antibacterial	Inhibits wound-associated pathogens
Angiogenic	Promotes blood vessel formation

Table 3. Components of plurethosomal nanocarriers

Component	Function
Phospholipids	Vesicle formation
Ethanol	Enhances membrane fluidity
Pluronic polymers	Provides deformability and stability
Water	Hydration medium

Table 4. Characterization parameters of plurethosomes

Parameter	Significance
Particle Size	Determines penetration ability
Zeta Potential	Indicates colloidal stability
Entrapment Efficiency	Measures drug loading
PDI	Shows uniformity of vesicle size

Table 5. Advantages and limitations of plurethosomal systems

Advantages	Limitations
Enhanced penetration	Possible ethanol irritation
Controlled release	Complex manufacturing
High stability	Regulatory challenges
Improved bioavailability	Scale-up difficulties

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